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EXAMINER

EPPERSON, JON D

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 01/05/2004

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

File Copy

Application No.

09/743,746

Applicant(s)

SCHMIDT ET AL.

Examiner

Jon D Epperson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 3, 13-19, 23-30 and 35-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4-12, 20-22 and 31-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on September 23, 2003 (Paper No. 14).

Priority Claims

2. The priority filing date of July 13, 1998 for United Kingdom 9815163.2 is acknowledged.

Status of the Claims

3. Claims 1-39 are pending in the present application.
4. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 14 is acknowledged (i.e., Applicants elected Group I, claims 1-34) and claims 35-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., Response to Restriction and/or Election of Species).
5. Please note: Applicant's elected species (Subgroup II = method of cleavage in a mass spectrometer; Subgroup III = method of identifying a reporter using a mass spectrometer) was found in the art. Furthermore, Applicant's *specifically* elected species (Subgroup I = FT134) was

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searched and was not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02

(emphasis added):

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

6. Claims 3, 13-19 and 23-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 6 (see below i.e., *Response to Restriction and/or Election of Species*).

7. Therefore, claims 1-2, 4-12, 20-22 and 31-34 are examined on the merits in this action.

Response to Restriction and/or Election of Species

8. Applicants' election without traverse of Group I (i.e., claims 1-34) in Paper No. 14 is acknowledged. Furthermore, Applicants' election of species without traverse in Paper No. 14 is also acknowledged.

9. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

10. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, “the list may not be incorporated into the specification but must be submitted in a separate paper.” Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

Specification

11. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

12. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant’s cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Objections to the Claims

13. Claim(s) 7-31 are objected to because of the following informalities:

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A. Claims 7-10, 14-31 and 33-34 are objected to under 37 CFR 1.75(c) as being improper form because a multiple dependent claim depends from another multiple dependent claim. See MPEP § 608.01(n). For compact prosecution any multiple dependent claim is treated as being dependent on the previous claim.

B. Claims 12, 13 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form or rewrite the claim(s) in independent form. Claims 12 and 13 depend from themselves, which cannot be further limiting.

Claims Rejections - 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claims 32-34 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-2, 4-12, 20-22 and 31-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method that employs “mass spectroscopy” with “compounds disclosed in claim 11” wherein “R¹ is a trifluoroacetyl group or methyl sulfate”, does not reasonably provide enablement for a method that employs “any” characterization method with “any” compound containing the formula shown in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This is an enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. Some of these factors may include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

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(1-2) Breadth of the claims and nature of the invention: The claims are drawn to a broad genus. The scope of this claim includes an infinite number of methods for providing and using an infinite number of compounds (i.e., structural variants of the formula represented in claim 1). Furthermore, the claims read on the use of an infinite number of detection methods. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: The instant specification only provides guidance to permit one of skill in the art to use the exemplified compounds in a mass spectrometer. Furthermore, only the compounds shown in claim 11 wherein R^1 = trifluoroacetyl group or methyl sulfate would be enabled because only these compounds possess a labile proton beta to the nitrogen that can support a negative charge as indicated in figure 9 to permit the facile release of the marker group for detection in a mass spectrometer. The Examiner further notes that Applicants do not provide any guidance for any other detection methods than mass spectroscopy. For example, Applicants do not disclose in their specification how these compounds could be "characterized" using EXAFS or SQUID, which would fall within the scope of Applicants' broad claims.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants' examples only involve compounds that contain the formula shown

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in claim 11 wherein R¹ is a trifluoracetyl group or methyl sulfate (e.g., see figures 3 and 15).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

16. Claims 1-2, 4-12, 20-22 and 31-34 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written

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Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claim 1 outlines method steps for characterizing a cleavable linker that binds a reporter and an analyte. The scope of this claim includes an infinite number of methods for producing and using an infinite number of structural variants (i.e., variants of the formula shown in claim 1) wherein no distinguishing structural attributes are provided the analyte or the reporter. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the analyte, reporter and analyte-linker-reporter. Although the specification discloses a few examples (e.g., see Specification, figures 3-15), the specification and claims do not provide any guidance as to what structural features all of these analytes, reporters and linkers share. Consequently, it is not possible to determine *a priori* which compounds would encompass because there is no common structural attributes that can link together all of the analytes, reporters and linkers i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* all the different types of compounds that should be included in this genus from the few examples provided by applicants.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify all of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing examples like FT134 (e.g., see specification, figure 11) is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails

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to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 1-2, 4-12, 20-22 and 31-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. *Claims 1-2, 4-12, 20-22 and 31-34* are rejected because the R, R', X and X' groups in these claims are not defined with any chemical or physical characteristic, but only by functional properties i.e., the ability to act as an analyte or a reporter. A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a group with this function. Thus, the metes and bounds of the claimed invention cannot be determined. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169.

B. For **claim 6**, the substituents "D" and "F" are vague and indefinite because it is not clear what "D" or "F" refers to. Applicants are requested to clarify and/or correct. Therefore, claims 6 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

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C. For **claim 7**, the phrase "a group selected from ... -NR¹-" is vague and indefinite because R¹ is not defined. Consequently, the metes and bounds of the claimed invention cannot be determined. Therefore, claims 7 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

D. For **claims 6, 12, 16, 19, 23**, Applicants use improper Markush format. It is suggested to use standard Markush language; see MPEP 2173.05(h) concerning alternative expressions:

Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925).

When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper.

Therefore, claims 6, 12, 16, 19, 23 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

E. For **claims 12 and 13**, the phrase "[a] method according to claim 12" or the phrase "[a] method according to claim 12 or claim 13" is vague and indefinite because it is not clear how claims 12 and 13 can be considered dependent claims when they do not depend from another claim. Therefore, claims 12, 13 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

F. For **claim 17**, the phrase wherein "m is 0 or 1 and the S atom attaching R⁷ to the linker is the sulfur atom of the cysteine group" is vague and indefinite because cysteine does not have an adjacent O (i.e., when m is 1), nor does it have a SO_n-CH₂-CH₂- group. Therefore, when m is 1, it would appear to the Examiner that the S cannot be the sulfur

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atom of a cysteine. Applicants are requested to clarify and/or correct. Therefore, claims 17 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

G. **Claims 32-34** provide for the "use" of linker groups with the formula disclosed in claim 32, but, since these claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. See MPEP § 2173.05(q).

H. For **claim 32**, the formula disclosed therein is vague and indefinite because the ends of the linker are not defined. If Applicants intend the ends of the linker to be methyl groups then it is not clear how the analyte and/or reporter group would be attached. Furthermore, the parenthesis appears to be superfluous because Applicants do not indicate that more than one $-\text{SO}_n\text{-CH}_2\text{-CH}_2\text{-}$ group can be used. Therefore, it is not clear what the parenthesis are used for. Therefore, claim 32 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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18. Claims 1, 2, 4-9, 11-12, 20 and 31-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Nothnagel (Nothnagel, E. A. "Synthesis and characterization of fluorescent Lucifer yellow-lipid conjugates" *Biochimica et Biophysica Acta* **1989**, 980(2), 209-219).

For *claim 1, 32-34*, Nothnagel (see entire document) discloses methods for synthesizing and using fluorescent Lucifer yellow-lipid conjugates (see Nothnagel, abstract), which anticipates claim 1. For example, Nothnagel discloses providing a compound in which the analyte is attached by a cleavable linker to a reporter group relatable to the analyte having the formula shown in claim 1 (e.g., see Nothnagel, figure 1, schematic B showing a compound with formula $LY-SO_2-CH_2-CH_2-DC_{12:0}PE$). In this scenario, the Lucifer Yellow Dye ("LY") represents the "reporter" and the $DC_{12:0}PE$ represents the "analyte." Nothnagel further discloses cleaving the reporter group from the analyte (e.g., see Nothnagel, figure 2 wherein the $DC_{12:0}PE$ "analyte" is cleaved from the LY "reporter" via FAB-MS i.e., the peak at 578 corresponds to the "cleaved" $DC_{12:0}PE$ analyte peak). Finally, Nothnagel discloses identifying the reporter group, thereby characterizing the analyte (e.g., see Nothnagel, figure 2 wherein the parent ion and fragment ions that contain the FY reporter are "identified" and used to "characterize" the lipid analyte via comparison of molecular weights). Please note that there are many other variations for the analyte and/or reporter that also read on Applicants' claims. For example, the "analyte" could be a "12:0 fatty acid side chain" instead of the $DC_{12:0}PE$ mentioned above or the phosphatidic acid portion ("PA") of the molecule (e.g., see

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Nothnagel, figure 2 wherein the peaks at 946 and 346 represent "lyso" derivatives of DC_{12:0}PE wherein fatty acid side chain "analytes" are cleaved from the reporter).

For *claim 2*, Nothnagel discloses a covalent linkage between the analyte and/or reporter group and the cleavable linker (e.g., see figure 2 showing the cleavage of a covalent bond when the DC_{12:0}PE signal is generated at mass 578).

For *claim 4-6*, Nothnagel discloses a substituted phenyl wherein R², R⁴, R⁵ and R⁶ are hydrogen and R³ is LY (e.g., see Nothnagel, figure 1, scheme B wherein a phenyl ring connects the LY to the SO₂-CH₂-CH₂-DC_{12:0}PE i.e., LY-phenyl-SO₂-CH₂-CH₂-DC_{12:0}PE).

For *claims 7-9*, Nothnagel discloses -NR¹- wherein R¹ is a hydrogen (e.g., see Nothnagel, figure 1, scheme B showing -SO₂-CH₂-CH₂-N(H)-CH₂-CH₂-).

For *claims 11-12*, Nothnagel discloses LY-phenyl-SO₂-CH₂-CH₂-N(H)-CH₂-CH₂-DC_{12:0}PA wherein "PA" represents the phosphatidic acid portion of the molecule (e.g., see Nothnagel, figure 1, scheme B). In this scenario, X' is PA, the "handle" connecting PA to N-R¹ is -CH₂-CH₂-, R¹ is hydrogen, the "handle" connecting SO₂ to X is a covalent bond and X is LY. Please note that claim 12 has been interpreted as depending on claim 11.

For *claims 20 and 31*, Nothnagel discloses detecting the reporter using FAB-MS and its cleavage products (e.g., see Nothnagel, figure 2).

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Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Jon D. Epperson, Ph.D.
December 29, 2003

BENNETT
PRIMARY EXAMINER

